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EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
1632	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/253,573	Applicant(s) CHEN, HAI XING	
	Examiner Richard Schnizer	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *30-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment was received and entered as Paper No. 12 on 3/27/01. Claims 1-29 are pending and under consideration.

Withdrawal of Finality of Previous Office Action

Applicant's arguments with regard to the finality of the previous Office Action, filed 3/27/01, have been fully considered but they are not persuasive. Applicant argues at page 13 and 14 of the response that the new ground of rejection in Paper No. 7 was not necessitated by amendment. This is unpersuasive in view of Applicant's admission at page 14 of the response that the amendment narrowed the scope of the rejected claims. In fact, the amended claim introduced several new limitations which were not present in the original claims. For example, the amended claims required a promoter which "is active only in progenitor cells of red blood cells" , whereas the original claims required only "a promoter". In response, a new rejection was set forth which was directed to the new limitations. This rejection was clearly necessitated by Applicant's amendment, thus the rejection was properly made final. See MPEP 706.07(a). Nonetheless, finality of the previous Office Action is withdrawn in view of the several new grounds of rejection set forth in this Office Action. In Paper No. 3, claims 1-29 were rejected under 35 USC 112, first paragraph as lacking enablement for therapeutic methods. This rejection was withdrawn in part in Paper No. 7. After further consideration of the intended use of the invention as set forth in the specification, a new ground of rejection is set forth below. Also

contained in this Office Action are new grounds of Rejection under 35 USC 112, second paragraph, and 35 USC 102.

Rejections Withdrawn

After further consideration, the rejections of claims 4, 11-15, 19, 25, and 26 under 35 USC 103 are withdrawn.

The rejections of claims 9 and 24 under 35 USC 112, second paragraph have been withdrawn in favor of new grounds of rejection.

Specification

The disclosure is objected to because it is contains spelling and grammatical errors. For example the proteins listed at page 6, lines 11 and 12, lack articles, as does "hemoglobin promoter" at line 27; "later" is misspelled on page 10, line 31; "Example" lacks an article on page 11, line 6; "hemaphilia" is misspelled at page 11, line 14, and "sag" is misspelled at page 12, line 11; "argumentation" is misspelled on page 13, line 8. This is a partial list. Applicant should thoroughly inspect the disclosure for errors and make corrections as appropriate.

Claim Objections

Claims 1-29 are objected to because they lack an article preceding the words "blood stream". It is also noted that "blood stream" should be condensed into a single word.

Claims 9 and 23 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. These claims fail to further limit their respective parent claims because the rupture must occur in the mammal. More specifically, parent claims 1 and 16 require rupture of red blood cells and release of the protein "into blood stream [sic] of said mammal".

Claims 10 and 24 objected to because each of these claims lacks an article preceding the words "life time". It is also noted that "life time" should be condensed into a single word.

Claims 13-15 are objected to because the phrase "any one of Claim 11-12" is ungrammatical. It is suggested that the phrase should be rewritten as "either one of claims 11 or 12".

Claims 27-29 are objected to because the phrase "any one of Claim 25-26" is ungrammatical. It is suggested that the phrase should be rewritten as "either one of claims 25 or 26". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is a method for producing and delivering protein *in vivo*. Claims 1-15 comprise delivering to progenitors of mammalian red blood cells isolated from a mammalian host an expression construct comprising a promoter operably linked to a gene encoding a protein which is not native to red blood cells. The transfected progenitors are then reintroduced into the mammalian host, wherein they give rise to red blood cells containing the desired protein. The red blood cells subsequently lyse, resulting in delivery of the protein. Lysis may be induced by genetic mutation. Claims 16-21 and 23-29 are similar to claims 1-15 except that the promoter must be a hemoglobin promoter, and the cells may be any mammalian cells derived from the host. In claim 22 the identity of the cells is restricted to "stem cells".

The asserted use of the invention is the delivery of therapeutic proteins. See page 10, lines 13-15; page 11, lines 10-20; page 13, lines 7-24; page 14, line 4 to page 16, line 1. The specification discloses that the claimed invention "has a broad scope of applications in treating diseases". See page 14, lines 4 and 5. Specific diseases which may be treated using the claimed invention including cystic fibrosis, Duchenne muscular dystrophy, hemophilia A, Huntington's disease, familial hypercholesterolemia, fragile-X syndrome, and cancer in general. See page 14,

lines 12-15 and paragraph bridging pages 14 and 15. The specification also considers treating diseases in general through the delivery of enzymes and hormones. See page 14, lines 15-30. The specification asserts no use for producing and delivering protein *in vivo* other than for the treatment of disease. For these reasons, in order to enable the invention for its intended use, the specification must teach how to use the invention for the treatment of the range of diseases set forth in the specification.

A review of the prior art shows that techniques for isolating, transfecting and successfully engrafting red blood cell precursors were established at the time of the invention. See US Patent 5,665,350, *e.g.* claims 2 and 4-6. It is also clear that this technique could be used to produce the encoded proteins. See e.g. Plavec et al (Blood 81(5):1384-1392, 3/1993), abstract. However, obtaining sufficient expression of proteins for therapeutic purposes is problematic. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by several review articles. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome

that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). The instant specification acknowledges the unpredictability of the art at page 1, lines 11-19, which indicates that "no approach has definitively improved the health of one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide."

Claims 16-29 require the use of a hemoglobin promoter to drive expression of the selected gene. Persons et al reviewed the history of attempted therapy of hemoglobin disorders by *ex vivo* transfection and reimplantation of red blood cell precursors. See Proc. Nat Acad. Sci. USA 97(10):5022-5024, 5/2000). This article emphasizes the difficulty in obtaining hemoglobin promoter-driven expression of proteins in red blood cell precursors, specifically citing problems with gene silencing and position effect variegation. See entire document especially paragraph bridging columns 1 and 2 on page 5022; column 2, line 21 through first full paragraph in column 3, page 5022. Thus prior to, and subsequent to, the time the invention was filed, those of skill in the art were unable to obtain therapeutic concentrations of proteins within red blood cells using hemoglobin promoters. The claimed invention requires delivery of proteins after lysis of red

blood cells, thus the problem of poor expression of protein is compounded by the problem of dilution into the blood stream. This necessarily lowers the concentration of the proteins and points to a need for far higher efficiency of expression than that obtained using hemoglobin promoters, because the specification fails to teach any method of targeting proteins to any specific tissue. The claimed mode of delivery also fails to account for the biology of some of the disorders it is intended to treat. For example, the specification teaches treatment of cystic fibrosis by supply of a desired protein. See page 14, lines 4-15. Cystic fibrosis is caused by a defective version of a transmembrane ion transporter, the cystic fibrosis transmembrane conductance regulator (CFTR), and the effect of the disease is manifested in the lungs. Certainly one could not expect to deliver a functional CFTR and expect it to spontaneously integrate into the appropriate alveolar membrane without the aid of a ribosome and from the extracellular side of the membrane. However, the specification provides no guidance or examples as to how one of skill in the art could treat this loss function by delivery through the blood of any desired protein.

The specification fails to identify specific proteins which should be used to treat a variety of the diseases which are asserted to be treatable with the instant invention, such as Huntington's disease, Gaucher's disease, familial hypercholesterolemia, and cystic fibrosis. Furthermore the specification fails to give any guidance whatsoever as to how much of any specific gene product would be required to treat any given disease, or how to obtain any specific dosage or

administration profile. It fails to teach how many cells should be delivered for any given treatment or how to protect released proteins from proteases present in the blood.

Claims 10 and 24, require that the rupture of red blood cells containing the expressed protein must be induced by genetic mutation of these cells. The specification fails to disclose a single example of any such mutation nor any guidance whatsoever as to what mutations will afford such an effect. Because these mutations are required by the claim, they must be considered to be critical elements of the invention. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identification of specific genes used to treat specific diseases, dosages of cells, expression profiles required to effect treatment, and mutations which induce lysis of red

blood cells cannot be considered minor details which can be omitted in the process of providing an enabling disclosure.

The claims also require that the expressed protein must be contained only in red blood cells. The specification describes a red blood cell as one which has no nucleus, thus the term red blood cell is understood by the PTO to refer to mature red blood cells. However the prior art teaches that proteins present in red blood cells, particularly those expressed from globin promoters, are expressed at all stages of erythroid cell differentiation. See e.g. Kim et al (Blood 47(5):767-776, 5/1976), abstract. Neither the prior art of record nor the specification provide any guidance or examples as to how to delay translation of mRNA until developing erythrocytes reach maturity. Thus one of skill in the art could not practice the invention as claimed.

Claims 16-21 and 23-29 embrace the production of red blood cells from any mammalian cell, or from any stem cell. It is well known in the art that red blood cells are produced from hematopoietic stem cells. Neither the prior art of record nor the specification provide any guidance or examples as to how to induce other cells not involved in the natural maturation of hematopoietic stem cells into red blood cells to differentiate into red blood cells as required by the claims. For example, neither the specification nor the prior art of record provide any guidance as to how to induce neural stem cells to differentiate into red blood cells. It is suggested that claims 16-21 and 23-29 should be amended to limit the identity of the cells to progenitors of red blood cells, as in claims 1-15 and 22.

Because the specification fails to teach how to treat any specific disease through the use of the claimed invention, much less the variety of diseases disclosed, because the prior art shows that gene therapy was highly unpredictable at the time of the invention, and because the specification fails to disclose mutations which can induce lysis of red blood cells or how to use them in the invention, one of skill in the art could not use the invention as intended by the specification, without undue experimentation.

Response to Arguments

Applicant's arguments filed 3/27/01 have been fully considered but they are not persuasive.

Applicant argues at page 3 of the response that they are responsible only for "enablement of the disclosed method within the scope defined by the claims, not beyond the scope of the claims." It is Applicant's position that gene therapy is not within the scope of the claims. This argument is unpersuasive because it is unsupported. The PTO has pointed to several passages in the specification which explicitly disclose that the invention is intended for use in gene therapy. See page 10, lines 13-15; page 11, lines 10-20; page 13, lines 7-24; page 14, line 4 to page 16, line 1. Furthermore, the PTO has established the position that the specification asserts no use for expressing proteins *in vivo* other than gene therapy, and Applicant has failed to point to any passage in the specification which contradicts this position. For these reasons, gene therapy is

clearly within the scope of the claims, and in fact there is no material other than gene therapy which the claims, when read in light of the specification, are clearly intended to encompass.

With respect to claims 10 and 24, Applicant argues that one is not required to disclose information which is well known in the art in order to provide an enabling disclosure. In an attempt to show that mutations which induce lysis of red blood cells are well known in the art Applicant submitted references in Paper No. 6 which list genes in which such mutations occur. Applicant's argument is unpersuasive for several reasons. First, because the mutations are required by the claim, they must be considered to be critical elements of the invention. As noted above, the failure to disclose critical elements of an invention results in a failure to meet the enablement requirement, regardless of whether or not the material was known in the prior art. See Genentech, Inc, v Novo Nordisk A/S, 42 USPQ2d 1001. Second, none of the references provided by Applicant disclose the precise nature of any of the mutations which could be used for this purpose, *i.e.* the nucleotide sequences which would be required in order to practice the invention are not disclosed, thus one of skill in the art would be required to determine empirically which mutations give the desired effect. Third, it noted that almost all of the mutations disclosed are recessive in nature, and Applicant has not taught how these mutations could be used in cells which also express the corresponding wild type gene. In the presence of one or more wild type alleles, these mutant genes would have no effect. Fourth, the problems with sustained gene expression which currently cripple the art of gene therapy would also apply to the only dominant mutation disclosed in the references. Applicant has not taught what level of

gene expression is required in order to achieve the lytic effect, how to obtain this level of expression, or how to sustain it. Thus, even if the lysis-inducing mutations were not critical elements of the invention, the specification and the prior art still fail to teach one of skill in the art how to use them within the context of the invention. Finally, Applicant has failed to make available any of these mutations, or cells comprising them, and has provided no guidance whatsoever in the process of generating such mutations or cells. For these reasons the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-29 are indefinite because the recited method steps are not concordant with the purpose set forth in the preamble. The claims recite methods of delivering a protein, but recite no step in which a protein is delivered.

Claims 1-29 are also indefinite because they recite "said protein" in step (d) without proper antecedent basis. The antecedents for "said protein" include the protein recited in the preamble, and the protein recited in step (a) of the claims. The term "protein" in the preamble is

not limited to any specific protein, such as the one recited in step (a), thus it is unclear to which antecedent the "protein" of step (d) refers.

In claims 1-15, the phrase "inserting a promoter and a gene encoding a non-native protein to red blood cells in a vector with an operable linkage between said promoter and said gene" is indefinite because it is confusing. The claim appears to require insertion of a promoter and a gene into a vector which already comprises a copy of the promoter and the gene. This would lead to a vector comprising two copies of the expression cassette. The specification does not contemplate such a construct. This phrase is also awkward. It is suggested that part (a) of the claim should be rewritten as follows: "(a) inserting into a vector a promoter which is active only in progenitor cells of red blood cells, and a gene encoding a protein which is not native to red blood cells, wherein said promoter and said gene are operably linked;". The claims are also confusing because the nature of the vector recited in step (c) is unclear. More specifically, step (c) requires transfecting cells with "said vector". The antecedent for said vector is recited in step (a), and corresponds to a vector used for insertion of an expression cassette, and not to the vector which results from insertion of the expression cassette. Thus transfection of cells with the vector recited in step (a) would not lead to expression of the desired protein in the cells, unless as noted above, the vector recited in step (a) already comprises a first such expression cassette. These claims also lack antecedent basis for "the treated progenitor cells". It is suggested that the word "transfected" should be substituted for the word "treated".

Claims 16-29 are indefinite because they call for insertion of a hemoglobin promoter and non-hemoglobin gene into a vector which already comprises these elements. These claims also lack antecedent basis for "the treated host cells". It is suggested that the word "transfected" should be substituted for the word "treated".

Claim 3 and 18 are indefinite because it is unclear what is intended by "natural promoter". This phrase could imply that the promoter used must have been isolated from a natural source, rather than synthesized by chemical means. Alternatively, it could simply mean that the sequence of the promoter is one that is found in nature. However, this second interpretation would also be indefinite because the sequences of natural promoters are constantly evolving. Because the genus of sequences of natural promoters is constantly changing, one of skill in the art could not be sure which sequences were embraced by the claims at the time of the invention.

Claims 4 and 19 are indefinite because they recite the term "mutated", which is a relative term that modifies the term "promoter". Neither the claims nor the specification set forth any standard reference "wild type" promoter against which one could compare another promoter in order to determine if it is "mutated". Furthermore, it is unclear if the use of the term mutated refers to a change in nucleotide sequence relative to a reference sequence, or whether the mutation must result in an assayable phenotype, and if so, what phenotype. Thus one of skill in the art cannot know which promoters are embraced by the claims.

Claim 5 is confusing because it refers to promoters which are native to red blood cells. As noted at page 11, line 3 of the specification, red blood cells comprise no nucleus, so there are no promoters which are native to red blood cells.

Claims 13 and 27 are indefinite because it is unclear what are the metes and bounds of the genus of "naturally-occurring" proteins. Because proteins are continually evolving, their sequences are constantly changing. Thus one of skill in the art could not know which protein sequences were embraced by the claims at the time of the invention.

Claims 15 and 29 are indefinite because they recite the term "mutated", which is a relative term that modifies the term "protein". Neither the claims nor the specification set forth any standard reference "wild type" protein against which one could compare another protein in order to determine if it is "mutated". Furthermore, it is unclear if the use of the term mutated refers to a change in amino acid sequence relative to a reference sequence, or whether the mutation must result in an assayable phenotype, and if so, what phenotype. Thus one of skill in the art cannot know which proteins are embraced by the claims.

Claims 16-29 are indefinite because they require a "hemoglobin promoter". There is no such thing as a hemoglobin promoter in the context of mammalian cells, and the specification fails to define the term. Hemoglobin is a tetrameric protein complex comprising for separate polypeptides of two different types. In adults, hemoglobin is composed of two alpha chains and two beta chains. The alpha and beta chains are encoded by separate genes on separate chromosomes under the control of separate promoters with distinct functional characteristics.

See for example, Voet et al, page 1142, column 2, first sentence of first full paragraph, and Humphries et al (Cell 30(1): 173-183, 8/1982), abstract. A search for the term "hemoglobin promoter" in the Medline database yielded only three hits, and these each referred to plant hemoglobin. Thus "hemoglobin promoter" is a term of art only in the context of plants, and not in the context of the instant invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 8, 9, 16-19, 22, 23, and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Hollis et al (US Patent 5,538,885, issued 7/23/96).

Hollis teaches a method of obtaining red blood cell progenitors from a mammal, transfecting them with a vector comprising a gene of interest under the control of either a hemoglobin promoter and enhancer, or a PLA2 promoter, and reintroducing the cells into the mammal. The encoded protein may be a hormone or an enzyme, and the protein may be retained intracellularly or secreted. Hollis teaches the use of a reduced form of the beta-globin promoter, which can be considered to be a mutated promoter. Hollis does not teach that red blood cells should lyse and release the protein into the blood. However, lysis of red blood cells is an

inherent property. Because Hollis teaches that the expressed proteins may be retained intracellularly, and because all red blood cells eventually lyse, Hollis anticipates the claims. See entire document, especially abstract, column 2, lines 7-17; column 3, lines 18-22 and 58-61; column 5, line 58 to column 6, line 3; sentence bridging columns 6 and 7; column 7, lines 24-47; column 8, lines 18-24; Example 2, column 13, line 47 to column 14, line 9; and Example 6, column 16, line 56 to column 17, line 40.

The disclosure of Hollis is considered to be enabling for the expression of proteins *in vivo* for the purpose of producing recombinant proteins as disclosed at column 8, lines 18-22, but not for therapeutic methods.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 7, 16, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hollis (1996) in view of Schlegel (US Patent 5,576,206, issued 11/19/96) and Wickham et al (US Patent 5,846,782, issued 12/8/98).

Hollis teaches a method of obtaining red blood cell progenitors from a mammal, transfecting them with a vector comprising a gene of interest under the control of either a

hemoglobin promoter and enhancer, or a PLA2 promoter, and reintroducing the cells into the mammal. See entire document, especially abstract, column 2, lines 7-17; column 3, lines 18-22 and 58-61; sentence bridging columns 6 and 7; column 7, lines 24-47; column 8, lines 18-24; Example 2, column 13, line 47 to column 14, line 9; and Example 6, column 16, line 56 to column 17, line 40.

Hollis does not teach the use of viral vectors for the transformation of red blood cell precursors.

Schlegel teaches a method of obtaining red blood cell precursors from an individual, transfecting them with a retroviral or adenoviral vector comprising an expression cassette for a gene of interest, and reintroducing the cells into the individual. See column 3, lines 22-36; column 5, lines 10 and 62-64; and column 7, lines 6-15.

Wickham teaches that lentivirus retroviral vectors are useful for gene transfer to hematopoietic cells. See column 11, lines 52-55; column 12, lines 29-31 and 41-44; and column 19, lines 14-18.

It would have been obvious to one of ordinary skill in the art to use an adenoviral, retroviral, or lentiviral vector in the invention of Hollis. One would have been motivated to do so because Schlegel teaches that adenoviral and retroviral vectors can be used to transfect red blood cell precursors, and because Wickham demonstrates that lentiviral vectors are useful for gene transfer to hematopoietic cells.

Thus the invention as a whole was *prima facie* obvious.

Response to Arguments

Applicant's arguments filed 3/27/01 have been fully considered but they are not persuasive.

Applicant's arguments with respect to the rejections of claims under 35 USC 102 and 103 are based on the central position that Hollis fails to teach a method of delivering protein by lysis of red blood cells. For support, Applicant notes that Hollis teaches a working example in which hGH is secreted from red blood cells, and that Hollis states that the appearance of hGH in the supernatant is due to secretion of the protein through the Golgi apparatus. Treatment of cells with brefeldin-A, which blocks flux through the Golgi led to no increase in hGH in supernatants. The inference appears to be that the invention of Hollis does not lead to release of hGH by rupture of red blood cells. This argument is unpersuasive because the example of Hollis was carried out *in vitro* on MEL cells, not on red blood cells. MEL cells are red blood cell precursors, not mature red blood cells. Applicant has failed to provide any evidence that suggests that the red blood cells of Hollis would not release proteins upon cellular lysis.

Applicant argues at page 8 of the response that Hollis teaches away from the instant invention because Hollis teaches delivery of proteins by the secretory pathway. This is unpersuasive because Applicant has failed to show that the proteins of Hollis would not also be released from red blood cells by the inherent action of cellular lysis at the end of the red blood cell's lifetime. Furthermore, Applicant's attention is directed to column 3, lines 20 and 21 which

indicate that expression of the proteins of Hollis need not be accompanied by secretion. Such proteins would clearly be released from the cells upon normal cellular lysis, thus Applicant's discussion of protein export pathways at page 8 of the specification is irrelevant. Applicant has failed to address this particular passage of the specification of Hollis.

Applicant argues at page 9 of the response that nothing would teach one skilled in the art that the natural result flowing from the teachings of Hollis would result in the Applicant's invention, and that one of skill in the art would not understand after viewing the Hollis disclosure that protein could be released from by rupture of red blood cells. Applicant further argues that the consequences of following Hollis does not always produce or result in Applicant's claimed invention. This argument is unpersuasive because it lacks support. Applicant has provided no evidence, for example, that those cells of Hollis which are designed to secrete proteins, would not also release protein upon cellular lysis. That is, Applicant has failed to show that the invention of Hollis would result in the clearance of all proteins from the secretory pathway prior to cell lysis. Furthermore, as noted above, column 3, lines 20 and 21 of Hollis indicate that the proteins need not be secreted. Applicant has provided no evidence or reasoning to suggest that these proteins would not be released by natural lysis, or that the red blood cells of Hollis do not undergo lysis.

Finally, it is noted that the claims do not require that the protein released by the cells must be the protein which is encoded by the recited gene. The claims are simply drawn to a "method for producing and delivering protein". It is not clear that the term "protein" refers to any one

specific protein. Thus, lysis of the cells of Hollis, followed by the release of hemoglobin, would anticipate the claims.

For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Patsy Zimmerman whose telephone number is 703-308-8338.

Richard Schnizer, Ph.D.

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER